UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/817,387	03/26/2001	Eckart Matthes	101195-24	9650

27387 7590 01/23/2006

NORRIS, MCLAUGHLIN & MARCUS, P.A.
875 THIRD AVE
18TH FLOOR
NEW YORK, NY 10022

EXAMINER	
EPPS FORD, JANET L	
ART UNIT	**PAPER NUMBER**
1633	

DATE MAILED: 01/23/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/817,387	MATTHES ET AL.	
	Examiner	Art Unit	
	Janet L. Epps-Ford	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 November 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12 and 14-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 14-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09/423,157.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

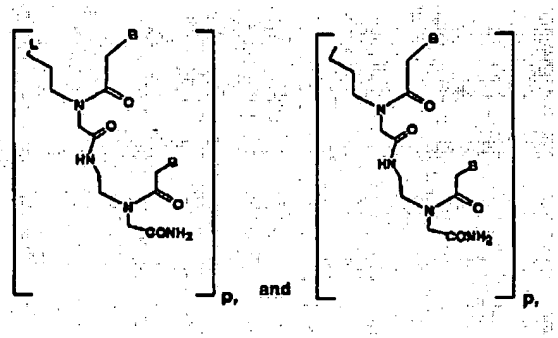
2. Applicants have amended claim 8 to recite SEQ ID NOs: 1-28. However, based upon the Applicant's election (4/01/2003) of the chimeric oligonucleotide described by SEQ ID NO: 16, the remaining sequences of SEQ ID NO: 1-15, and 17-28 have not been searched since they are drawn to a non-elected invention.

3. Claims 3-4 are rejoined per applicant's request set forth in the response filed 7-29-05.

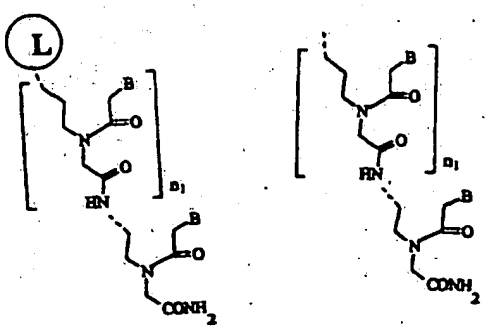
Claim Objections

4. Claims 1, 3-4 and 18 are objected to because of the following informalities:

Instant claim 1, claims 3-4, and claim 18 recite the following structures:



The above structures do not properly reflect the repeating structure set forth in the original claims. For example, original claim 1 recited the following repeating units:



Appropriate correction is required.

Response to Amendment

5. The Declaration under 37 CFR 1.132 filed 7-29-05 is insufficient to overcome the rejection of claims 8 and 12, and 14-15 based upon 35 USC § 112, first paragraph (scope of enablement) as set forth in the last Office action because: The experimental data provided by Applicants was not commensurate in scope with the claimed invention. The instant claims are drawn to an *in vivo* method of inhibiting the expression of telomerase activity in tumor cells in a mammal, wherein the scope of the claims encompass the therapeutic treatment of cancer. However, the Declaration evidence provides experimental data associated with a chimeric oligonucleotide consisting of a phosphorothioate modified part at the 5' end with a random sequence for binding to the primer binding site of telomerase protein and an antisense part that binds to the complementary sequence of the template region of the telomerase RNA, and further wherein the chimeric oligonucleotide comprises the following sequence 5'-d(ACTGCTCAGAGTTAGGGTTAG). The antisense was modified by N3'→P5' phosphoramidates or by 2'O-methylribonucleosides. However, the scope of the instant claims encompasses a plurality of antisense compounds that are not limited to those antisense compounds having the same structure as those used to produce the results set forth in Applicant's Rule 1.132 Declaration. Due to the unpredictability associated with the efficacy of antisense oligonucleotides in therapeutic treatments, there is no clear correlation between the efficacy of those particular compounds used by

Applicant's to produce a reduction in telomerase activity of 25-50% and 36-60% as set forth in the Table provided in Applicant's Declaration. It is noted that the instant claims, since practiced *in vivo,* and as contemplated in the specification as filed at page 14, last two lines, encompasses the therapeutic treatment of cancer in a patient. However, Applicant's results do not provide any evidence of a reduction in the number of tumor cells in a patient as a result of treatment with the exemplified antisense oligonucleotides. Applicants have not clearly set forth a direct correlation between the reduction in % Telomerase Activity, and the amelioration of cancer (i.e. a reduction in tumor size), set forth in the Declaration. Therefore, for the above reasons, Applicant's Declaration is inefficient to overcome the pending rejection.

Response to Arguments

Claim Rejections - 35 USC § 112

6. Claims 8, and 12, 14-15 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for using chimeric oligonucleotides according to the present invention to inhibit telomerase activity *in vitro* comprising the administration of chimeric oligonucleotides, and provides guidance for inhibiting telomerase activity in human cancer cells transplanted into a nude mouse, does not reasonably provide enablement for using chimeric oligonucleotides of undefined structure and/or target, *in vivo* for treating cancer in all non-human mammals. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

7. Applicant's arguments filed 7-29-05 have been fully considered but they are not persuasive. Applicants traversed the instant rejection by way of amending claim 8 to recite a method of inhibiting telomerase activity in tumor cells in a mammal, wherein the oligonucleotides have a nucleotide sequence selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 28. Additionally, Applicants state that the Declaration provided Exhibit 1, states in part, that based on the teachings of the specification and what was known in the art at the time of filing, one of ordinary skill in the art would have been able to use the claimed oligonucleotide compounds in a method for inhibiting telomerase activity in tumor cells in a mammal without undue experimentation. However, contrary to Applicant's assertions, an opinion declaration is inefficient to establish actual evidence of full enablement of the claimed invention as of the filing date of the instant invention. Moreover, Applicant's argue that the Declaration provided as Exhibit 2 provides a summary of an experiment that shows using the chimeric oligonucleotides according to the present invention to inhibit telomerase activity in human cancer cells transplanted into a nude mouse. The examiner agrees that the Exhibit demonstrates enablement of the scope of the claimed invention that encompasses the inhibition of telomerase activity in human cancer cells transplanted into the flank region of a nude mouse, comprising the specific administration of:

5'-d(ACTGCTCAGA-GTTAGGGTTAG) 10mer/PS/T11/PAM
5'-d(ACTGCTCAGA-GTTAGGGTTAG) 10mer/PS/T11/Ome

Moreover, Applicants argue that based upon MPEP § 2164.03, they have provided a correlation between their *in vitro* data and the production of *in vivo* results. However, it was well known in the art, as taught by Chirila et al. (2002), Jen et al. (2002), and Stein (2000), that at the time of the instant invention, there is significant level of unpredictability associated with the behavior of antisense based oligonucleotides *in vivo.* Contrary to Applicant's assertions, in the unpredictable field of antisense therapy, the disclosure of the ability of one particular sequence to function successfully to inhibit telomerase, specifically, SEQ ID NO: 28 and 23, is not sufficient to provide evidence of the ability of other compounds comprising a distinct sequence and modification to inhibit the expression of telomerase in a tumor cell in vivo, comprising a non-specific route of antisense administration.

Additionally, it is noted that the scope of the present invention now reads on any mammal, human and non-human mammal. Applicants have not provided sufficient guidance and/or instruction that would allow the skilled artisan to use the oligonucleotide compounds according to the present invention in a method for the treatment of conditions associated with telomerase activity, for example cancer, in any non-human animal, other than in transplanted human cells in a nude mouse.

As stated in the prior Office Action, Chirila et al. (2002), Jen et al. (2000), and Stein (2000) teach that the behavior of oligonucleotide based compositions and their delivery *in vivo* are unpredictable, therefore claims to pharmaceutical compositions and methods of treating diseases by the administration of oligonucleotide based pharmaceuticals are subject to the question of enablement due to the high level of

unpredictability associated with this technique as taught in the prior art. It was also previously stated that the quantity of experimentation required to practice the invention as claimed would require determining modes of delivery in a whole organism such that an undefined target nucleic acid is inhibited and the desired secondary effect of treating tumors is obtained. The specification as filed provides no specific guidelines in this regard; the specification merely provides a prophetic example for using the claimed compositions *in vivo*.

Furthermore, the evidence provided in Exhibit 2 was specifically limited to tumor cells that were subcutaneously injected to into the flank area of a nude mouse, and wherein administration of the oligonucleotide was via an intraperitoneal route. The instant claims are not limited to the treatment of subcutaneous tumors via an intraperitoneal route. The results provided in the Declaration do not provide any evidence of the reduction of any particular therapeutic effect. There is no evidence that there was any correlation between the observed inhibition of telomerase expression and a corresponding reduction in tumor size.

This conclusion is based upon the known unpredictability regarding the behavior of oligonucleotide compositions in a cell, delivery of antisense *in vivo,* irrelevant cleavage of non-specific targets, the quantity of experimentation required to practice the full scope of the claimed invention (which reads on the therapeutic use of the claimed pharmaceutical composition) and the lack of guidance thereof in the specification as filed in this regard.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 1-2, remain rejected and claims 5, 9-11 and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Uhlmann et al. for the reasons of record set forth Office Action mailed 11-17-03.

10. Applicant's arguments filed 7-29-05 have been fully considered but they are not persuasive. Applicants argue that the structures of Uhlmann et al. do not anticipate the claimed chimeric oligonucleotides since the 3' end of the instant structures comprise an primary amine, and those compounds of Uhlmann et al. are terminated by a secondary amide, and furthermore do not meet the requisite number of subunits.

11. However, contrary to Applicant's assertions it is noted that Applicants have not addressed the arguments set forth in the prior Office Action. As stated previously, the instant claims encompass wherein the full length oligonucleotide is an DNA molecule, wherein R3 is O, and R4 is 2'-deoxyguanosine, 2'-deoxyadenosine, 2'-deoxycytosine, or 2'-deoxythymidine. Absent evidence to the contrary, since the compounds of Uhlmann et al. are at least 10 nucleotides and not more than 20 nucleotides in length, the compounds of Uhlmann et al. encompasses the requisite number of n and p repeats as set forth in the structure of the chimeric oligonucleotides recited in the instant claims. Moreover, since the compounds recited in Uhlmann et al. meet the structural limitations

of the instant claims, absent evidence to the contrary, the compounds of Uhlmann et al. would also possess the functional characteristics of the compounds of the claimed invention. See MPEP § 2112[R-2]III. Where applicant claims a composition in terms of a function, property or characteristic and the composition of the prior art is the same as that of the claim but the function is not explicitly disclosed by the reference, the examiner may make a rejection under both 35 U.S.C. 102 and 103.

New Grounds of Rejection:

Claim Rejections - 35 USC § 112

12. Claims 1-5, 7, 9-12, 14-15, and 17-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for :

utilizing chimeric PNA (see SEQ ID NO: 1-28) oligonucleotides targeting the template region of telomerase RNA to inhibit telomerase activity *in vitro* or using phosphorothioate modified oligomers to non-specifically inhibit telomerase activity;

does not reasonably provide enablement for using any generic non-phosphorothioate containing oligomeric compound of undefined sequence structure to inhibit telomerase activity. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to:

(A) The breadth of the claims;

(B) The nature of the invention;

(C) The state of the prior art;

(D) The level of one of ordinary skill;

(E) The level of predictability in the art;

(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent application coupled with information known in the art without undue experimentation.

The breadth of the claimed invention encompasses the use of a broad genus of chimeric oligonucleotides, of undefined sequence, and comprising numerous structural permutations. According to the specification as filed at page 4, 4th paragraph:

> Antisense oligomers in which the sugar phosphate backbone is replaced by N(2-amino ethyl) glycine (peptide nucleic acids, PNA) were described to inhibit the telomerase in vitro at nanomolecular range (Norton et al., 1996). Here agein, the template region of telomerase RNA was used as target. However, it is also known from these excellently binding PNAs that they, could not be taken up by cell membranes whicvh limits their applicability (Hanvey et al., 1992). In the same paper Norton et al. reported that oligonucleotides modified by phosphorothioates are efficient, but non-specific inhibitors of telomerase.

Applicant's own specification indicate the necessity of replacing the sugar phosphate backbone with either phosphorothioates for non-specific telomerase enzyme binding or designing oligomers to comprise N(2-amino ethyl)glycine targeting the template region of telomerase RNA to reduce telomerase activity in vitro. However, it is also noted above that the N(2-amino ethyl)glycine modified oligomers could not be taken up by cell membranes.

Moreover, according to Applicants in order to overcome this problem their invention is drawn to chimeric oligonucleotides that comprise both of the above aspects, namely a protein binding site, and a region that binds RNA, see page 5, paragraphs 3-6.

Since the claimed structures do not require the presence of phosphorothioate modifications or the presence of a N(2-amino ethyl)glycine region targeting the template region of telomerase RNA, the scope of the claims therefore reads on oligonucleotides comprising a full sugar phosphate backbone, and further wherein the oligonucleotide is capable of inhibiting telomerase activity. However, other than those chimeric oligonucleotides that comprise both of the above aspects, namely a protein binding site, and a region that binds RNA, see page 5, paragraphs 3-6, and specifically those exemplified as SEQ ID NO: 1-28, Applicants have not provided sufficient guidance and/or instruction for the skilled artisan to use the full scope of the claimed oligonucleotides in a method to inhibit telomerase activity without undue experimentation.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford whose telephone number is 571-272-0757. The examiner can normally be reached on M-F, 9:00 AM through 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave T. Nguyen can be reached on 517-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Janet L. Epps-Ford
Primary Examiner
Art Unit 1633

JLE